Rivaroxaban-induced skin necrosis: a case report

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European Journal of Medical Case Reports
Volume 3(3):112–115

https://doi.org/10.24911/ejmcr/173-1555632293

ABSTRACT

Background: Even though rivaroxaban has been mainly associated with hemorrhage-related adverse effects, rivaroxaban-induced skin necrosis has received less attention or went unrecognized. Little has been documented about hypersensitivity reactions caused by the treatment with rivaroxaban.

Case Presentation: This paper reports a skin necrosis with an apparent similarity to skin adverse events caused by the different anticoagulants. It happened in a 30-year-old female patient during rivaroxaban treatment. The correlation of the skin lesions to the used drug was made by the act of repeated discontinuation and reuse of rivaroxaban and the noticed remission and exacerbation of skin necrosis.

Conclusion: This case highlights the vigilance required by healthcare in recognizing potential adverse effects of newly marketed drugs and in making medication changes whenever necessary.

Keywords: Rivaroxaban, adverse effects, anaphylaxis, hypersensitivity, skin necrosis.

Received: 25 April 2019 **Accepted:** 01 November 2019

Type of Article: Case Report **Specialty:** Vascular Surgery and Dermatology

Funding: None

Conflict of interests: None

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Background

Direct oral anticoagulants (DOACs) have predictable anticoagulant effect in the form of the ability to administer fixed doses without a need for routine anticoagulant monitoring, fast onset and offset of action, and relatively low potential for food and drug interactions compared to warfarin. Therefore, DOACs have broadened the options for anticoagulation and have been widely used since 2011 [1–3]. Rivaroxaban is an anti-factor Xa DOAC used for the prevention of thromboembolic complications in patients with non-valvular atrial fibrillation, for prophylaxis of deep venous thrombosis (DVT) in patients undergoing knee or hip surgery, and for acute treatment and secondary prevention of DVT and pulmonary embolism [4]. It is also approved by the European Medicines Agency, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after acute coronary syndrome with elevated cardiac biomarkers [5]. Due to the mechanism of action of rivaroxaban, much consideration has been given to hemorrhage-related adverse effects; thus, non-hemorrhage adverse effects receive less attention and some of them go unrecognized. The aim of this report is to present one of the non-hemorrhage-related adverse effects of rivaroxaban and to get a correct differential diagnosis of skin side effects during the anticoagulation therapy.

Case Presentation

A 30-year-old female patient has no significant relevant history apart from proximal femoral vein thrombosis. During the anticoagulation therapy, the patient started 30 mg rivaroxaban daily. Three days into therapy, the patient developed black and dark blue large patches ranging from 5 to 20 cm on the anterior, lateral, and posterior surface of her thighs as well as the anterior, lateral, and posterior surface of her legs and also in the left arm. Moreover, tense, sero-hemorrhagic blisters developed on both legs (Figures 1 and 2). No lesions were observed on mucosae or other parts of the body.

The patient was followed in the vascular surgery clinic service. The tentative diagnosis was that of a hypersensitivity or skin necrosis secondary to drug use. Rivaroxaban therapy was stopped for 3 days and switched to low molecular weight heparin (LMWH) in a dose of 1 mg/kg twice daily in addition to topical corticosteroid, betamethasone cream twice a day for 1 week. During the LMWH heparin treatment, no further episodes of skin necrosis were noticed. However, following another switch back to rivaroxaban, a new patch of skin necrosis ensued at a different site yet over a wider area. Once more, rivaroxaban was stopped and LMWH introduced instead with withdrawal of all other medications like venotonics and anti-inflammatory agents to provoke a more profound episode ensuring its direct relation to the DOAC in use. The patient was maintained on LMWH for 3 months until the duplex study confirmed the total resolution of popliteal DVT where treatment was discontinued apart from topical skin regenerating agents.

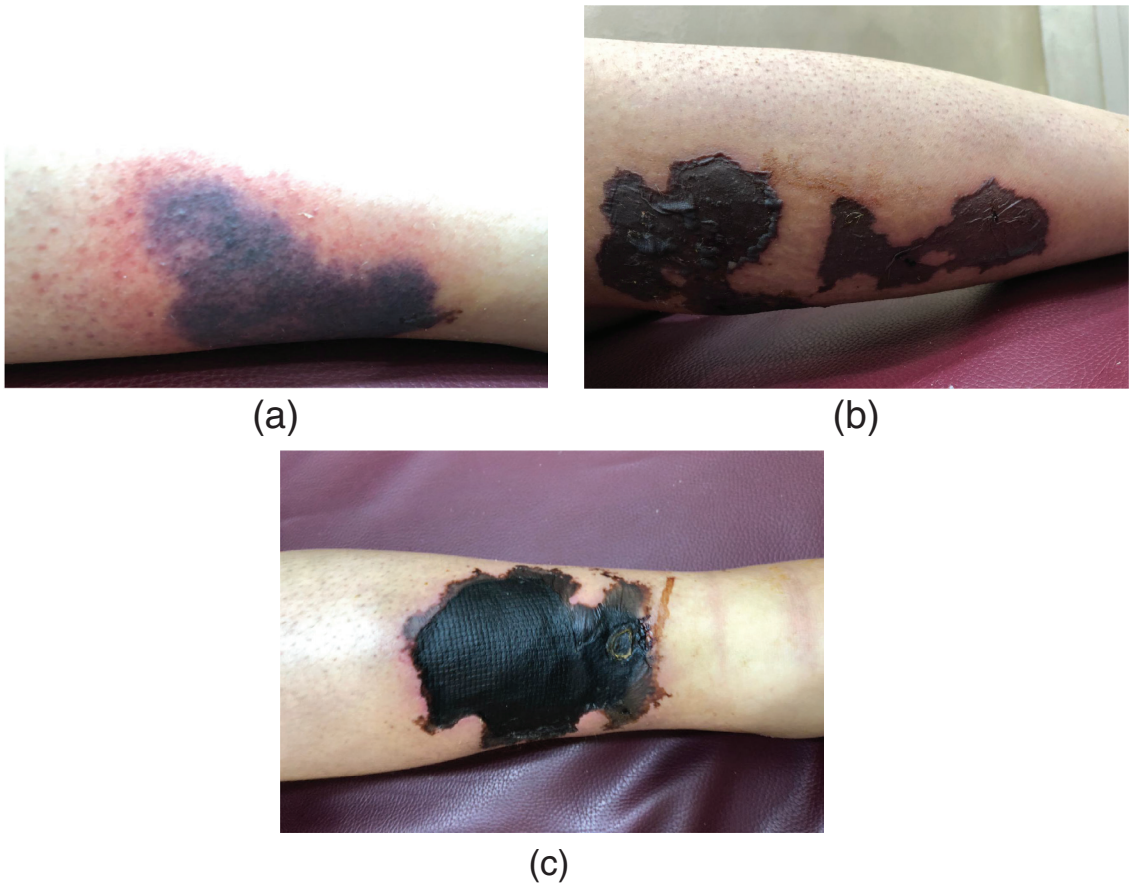

Figure 1. *(a). Black and dark blue large patches over the lateral aspect of the right thigh. (b). Multiple large black patches over the back of the right leg. (c). Large black patch over the anterior, medial and lateral aspects of the left leg.*

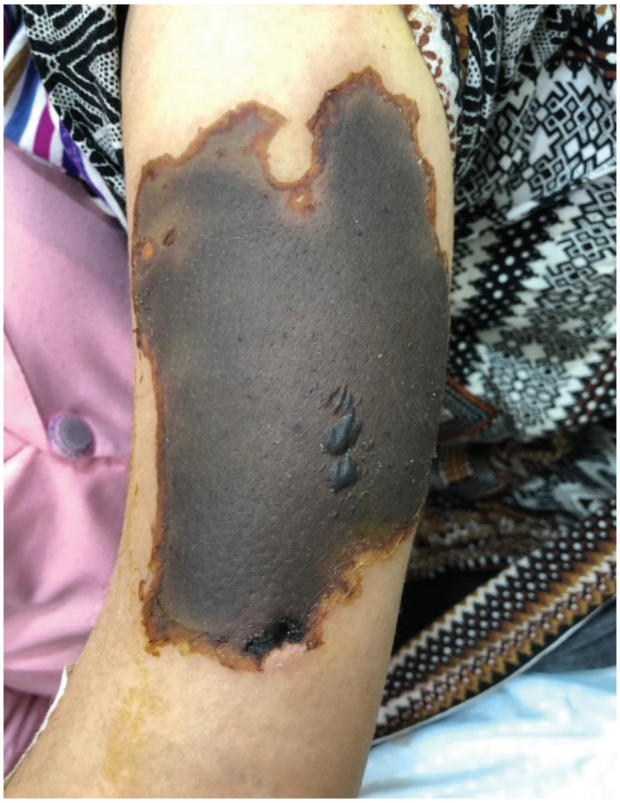

Figure 2. *(a) A large black patch over the left arm. (b) Multiple large black patches over the back of the right leg.*

The patient's work-up was as follows: white blood cells (WBC) of 5,000 with 0% eosinophils, platelets 190,000/µl, thyroid-stimulating hormone 1.19 IU/ml and rheumatoid factor 1/32, antinuclear antibody 21 IU/ml, and double-stranded DNA 5.90 IU/ml. The carcinoembryonic antigen 15-3 and CA 125 results were within normal ranges. The search for anti-skin, anti-basement, and epidermal membrane autoantibodies (indirect immunofluorescence) in peripheral blood was negative.

Discussion

The diagnosis of skin necrosis due to rivaroxaban was established clinically. Our differential diagnoses included hemorrhagic toxic necrolysis, heparin-induced thrombocytopenia, hypersensitivity, and Stevens–Johnson syndrome. Rivaroxaban was reported to cause generalized urticaria, erythema, severe pruritus, and angioedema of the orbital area and lips [6]. It is also reported to induce acute generalized exanthematous pustulosis in the groin within 48 hours of commencing therapy then spread over the body and face within a week with elevated WBC, neutrophilia and eosinophilia in the absence of infection [7]. However, in the present case, there was normal platelet count, absence of leukocytosis, and eosinophilia with negative results of the direct immunofluorescence test.

Negative immunofluorescence studies, as in this case, occur in 4% of the patients with hypersensitivity [8].

Cutaneous reactions have been reported during anticoagulant therapy with coumarin derivatives and with unfractionated and LMWHs and heparinoids [9–11]. However, very few data regarding skin necrosis due to rivaroxaban are available and only listed as a hypersensitivity reaction [12]. Even though heparins, warfarin, and rivaroxaban have very different mechanisms of action, the clinical similarity of their epithelial side effects is remarkable. In spite of this similarity, a differential diagnosis between the offending agents can be made with high confidence. Also, the neoplastic markers were of negative results.

As the rivaroxaban-induced skin necrosis (RISN), the warfarin-induced skin necrosis (WISN) as a complication of warfarin usage is uncommon. Typically, lesions develop during the first days after initiation of warfarin therapy (usually around the tenth day) and are often associated with the administration of a loading dose.

The pathophysiological mechanisms for RISN are uncertain although it may be like WISN, related to microvascular thrombosis, hypersensitivity, a direct toxic effect of the drug or an imbalance between the anticoagulant-procoagulant system [13].

RISN differs from WISN in that WISN lesions first present as erythematous rash single or multiple poorly demarcated at areas of high fat like breasts, buttocks, thighs, arms, hands, fingers, legs, feet, face, and abdomen and often associated with soft tissue edema and paresthesias. It might appear as petechiae progressing within hours to ecchymosis and large hemorrhagic blisters that turn into a frank necrosis but for the RISN in this case the lesions were large, multiple, sharply demarcated black colored, painless, and more at the lower limbs with small-sized blisters and no ecchymosis [14].

Conclusions

Since its release in 2011, RISN has not been reported. Mainly, they referred to liver injury, hypersensitivity reactions, leukocytoclastic vasculitis, skin necrosis, and hair loss. Clinicians must be aware of these adverse reactions and advise their patients to contact them as soon as they observe any unexpected clinical response. However, careful post-marketing surveillance should be continued in order to establish actual event rates.

Acknowledgment

The authors are very grateful for Dr. Mervat Soliman (consultant of immunology at Mansoura nephrology and urology center) for her valuable advice in the course of management of the present case.

List of Abbreviations

CA 125	Cancer antigen 125
WBC	white blood cells

Consent for publication

A written consent for publication was obtained from the patient.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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References

1. Comerota AJ, Ramacciotti E. A comprehensive overview of direct oral anticoagulants for the management of venous thromboembolism. Am J Med Sci. 2016;352(1):92–106. https://doi.org/10.1016/j.amjms.2016.03.018
2. Bauer KA. Pros and cons of new oral anticoagulants. Hematology Am Soc Hematol Educ Program. 2013;1:464–70. https://doi.org/10.1182/asheducation-2013.1.464
3. Conway SE, Hwang AY, Ponte CD, Gums JG. Laboratory and clinical monitoring of direct acting oral anticoagulants: what clinicians need to know. Am Coll Clin Pharmacol Pharmacother. 2017;37(2):236–48. https://doi.org/10.1002/phar.1884
4. Xarelto Package Insert Information [cited 2017 Nov 11]. Available from: https://www.xareltohcp.com /shared/product/xarelto/prescribing-information.pdf
5. Xarelto EMEA Product Information [cited 2017 Nov 11]. Available from: http:// www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000944/human_ med_001155.jsp
6. Altin C, Ozturkeri OAY, Gezmis E, Askin U. Angioedema due to the new oral anticoagulant rivaroxaban. Ann Cardiac Anaesth. 2014;17(2):173–4. https://doi.org/10.4103/0971-9784.129888
7. Vu TT, Gooderham M. Adverse drug reactions and cutaneous manifestations associated with anticoagulation. J Cutan Med Surg. 2017;21(6):540–50. https://doi.org/10.1177/1203475417716364
8. Calonje JE, Brenn T, Lazar A, McKee PH. McKee's pathology of the skin. 4th ed. vol. 1. Philadelphia: Elsevier Saunders; 2012.
9. Maldonado Cid P, Alonso de Celada RM, Noguera Morel L, Feito-Rodríguez M, Gómez-Fernández C, Herranz Pinto P. Cutaneous adverse events associated with heparin. Clin Exp Dermatol. 2012;37:707–11. https://doi.org/10.1111/j.1365-2230.2012.04395.x
10. Scherer K, Tsakiris DA, Bircher AJ. Hypersensitivity reactions to anticoagulant drugs. Curr Pharm Design. 2008;14:2863–73. https://doi.org/10.2174/138161208786369768
11. Bircher AJ, Harr T, Hohenstein L, Tsakiris D. Hypersensitivity reactions to anticoagulant drugs: diagnosis and management options. Allergy. 2006;61:1432–40. https://doi.org/10.1111/j.1398-9995.2006.01227.x
12. Vernon HM, Nielsen AK, O'Bryan EC. Hypersensitivity reaction after administration of rivaroxaban (Xarelto). Am J Emerg Med. 2016;34:1325.e1–2. https://doi.org/10.1016/j.ajem.2015.12.021

13. Fawaz B, Candelario NM, Rochet N, Tran C, Brau C. Warfarin-induced skin necrosis following heparin-induced thrombocytopenia. Proceedings (Baylor University Medical Center). 2016;29(1):60–1. https://doi.org/10.1080/08998280.2016.11929362

14. Nazarian RM, Van Cott EM, Zembowicz A, Duncan LM. Warfarin-induced skin necrosis. J Am Acad Dermatol. 2009;61(2):325–32. https://doi.org/10.1016/j.jaad.2008.12.039

Summary of the case

1	**Patient (gender, age)**	A 30-year-old female
2	**Final Diagnosis**	hypersensitivity or skin necrosis secondary to rivaroxaban drug therapy
3	**Symptoms**	The patient was treated with rivaroxaban for left iliofemoral deep vein thrombosis. Three days into therapy, the patient developed black and dark blue large patches ranging from 5 to 20 cm on the anterior, lateral, and posterior surface of her thighs and legs.
4	**Medications**	The patient received rivaroxaban alternating with LMWH when skin necrosis developed.
5	**Clinical Procedure**	Discontinuation of the offending treatment and continuation on LMWH resulted in ceasing of the skin lesions. The whole clinical situation was repeated when drug interchange was tried.
6	**Specialty**	Vascular surgery and dermatology.